PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

Supplement Number: Supplement Type:	0898 Trade Nam Generic Name: Dosage Form: Proposed Indication:	THYROTROPIN ALFA Injectable: Intramuscular An adjunctive diagnostic tool for serum thyroglobulin (Tg) testing with or without
IS THERE PED	IATRIC CONTI	ENT IN THIS SUBMISSION? YES
Ne Inf	oNates (0-30 Days ants (1-24 Months er Age Groups (lis	years) Adolescents (13-16 Years)
Label Status Formulation Sta Studies Needed Study Status	tus <u>NEW FOR</u> <u>STUDIES 1</u>	MATE Labeling for ALL PEDIATRIC ages MULATION developed with this submission needed. Applicant has COMMITTED to doing them re submitted and approved
Are there any Pedia Submission? YES	atric Phase 4 Comm	itments in the Action Letter for the Original
COMMENTS: Thyroid cancer is unfor this population (common in the pedia November 24,, 1998)	stric population. Therefore, pediatric studies are not required
No pediatric plan sub	omitted.	
This Page was comp SAFETY OFFICER	oleted based on info	rmation from a PROJECT MANAGER/CONSUMER ORT
Signature		11-24-58
		Date Date

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

_May 20, 1998

FROM:

Jean Temeck, M.D.

NDA:

20-898

SUBJECT:

Pediatric Labeling

TO:

File for NDA 20-898; Thyrogen

Thyroid cancer is uncommon in pediatric age patients, Therefore pediatric studies are not required for this population.

Jean Temeck, Medical Officer

HFD-510

THE WAY

September 13, 1998 Memorandum

To: the File NDA 20-898, Thyrogen (thyrotropin alpha) From: Solomon Sobel M.D. Directors Division Metabolic and

Endocrine Drug Products

Subject: Approvable letter

There are several issues which must be resolved before a final

- 1. Final labeling: There will be refinements in the DESCRIPTION section of the labeling in respect to the designated potency. At present the assigned potency of may have to be modified
- 2. Submission of protocol for the determination of a reference
- 3. Clear delineation of what will constitute the release specification in respect to potency

There are several other issues which have arisen during our review in the areas of pharmacokinetics and statistics which I believe do not have to be addressed before final approval is

Pharmacokinetic reviewer:

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			그는 그가 그러 하는 그리가 된 것으로 되는데 이번을 한다고 있다고 있다. 그 나는 그는 그는 그를 가지를 갖는 때문에 되었다는데 하는데 되었다.
			사람들이다. 우리는 그리다는 회사님은 그리는 그리는 학생들이 되는 것이 되는 것이 되었다. 스토트 전문을 받는 사람들이 되었다.
			하는 어느 하는 아이들 아이들은 사람들은 사람들이 되었다. 그는 사람들은 사람들이 하는 사람들이 되었다. 그는 사람들이 되었다.
			그 하다 하는 사람들은 음식이 되는 것이 되는 일반을 하는 하고 있는데 말이 되고 있는데 하는데 하는데 하다 되었다. 그 그 그는 밤
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			그는 항상 시간에서 회사는 원리에게 하는 것이 되었다. 회사를 보면 한 것은 사람들이 되는 회사를 하는 것은 사람들이 살았다. 그는 그 그는 그
			그 하지만 않는 눈이 있다면 되는 사람들은 살이 가장 없는 것이 하는 것이 하는 것이 하는 것이 하면 하는 것이 하면 하는 것이다.
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			그는 하는 사람들은 사람들은 살아들이 있다. 아름이 살아 아름이 살아 아름이 살아 아름이 살아 나를 살아 하는데 살아 살아 살아 나를 살아
			그가 되는 그리면 한 문제를 모든 모든 이 집에서 그리다는 그리고 있는 이 집에 한 집에 되는 것이 되었다면 하다 하다.
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			그리는 사람들은 사람들은 어디에 가장 아니는 사람들이 되었다. 그 사람들은 사람들은 사람들은 사람들은 사람들은 사람들은 사람들이 되었다.
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			그런데 금액은 어느는 작업으로 나는 그리네트 전에 되었다면 말을 받았다는 것은 생각이 되었다. 그리고 그리고 되었다.
1. 15			그는 나는 사람들은 살아보고 있는 경험 사람들이 들어 들었다. 그는 사람들이 되는 사람들이 가는 사람들이 되었다. 그는 사람들이 하는 것이다.
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			요 있는 사람들이 가지 않는 아이들은 사람들은 사람들이 되었다. 그는 사람들이 하는 사람들이 가지 않는 것이 없었다. 그는 사람들이 가장 하는 것이다.
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			사고, 생생님, 나는 생생님 때문에 가장 없는 사람들이 되었다. 그는 사람들이 되었다면 하는 것이 되었다면 하는 것이 없는 것이 없는 것이 없다면 하는데 없다면 없다면 없다면 없다면 없다면 없다면 사람들이 되었다면 없다면 없다면 없다면 없다면 없다면 없다면 없다면 없다면 없다면 없
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Statistical review:

The statistical reviewer believes there may have been significant bias introduced by the fact that the scans were read as a couplet. (that is the Thyrogen scan was read paired with the Fither this was a patient).

Either this was a direct side by side comparison or the scans were read sequentially with the reader maintainining a sufficient memory of the previous reading.

The bias may be one of wanting to establish equivalence of reading since this might be viewed as the "desirable" outcome.

There is merit to this criticism. However, this possible bias appears to be a remote determinant in these studies. The films were read by three independent reviewers and there was a procedure for discordance arbitration. It is also difficult to determine the direction of the bias; one might argue that the bias would work to establish concordance. However, there is also a possibility that the availability of comparison scans might induce a greater tendency to note discordancies in such issues as extent of disease.

In any event these ideas were presented to our Advisory Committee and they discounted them.

Conclusion: The Division recommends an approvable letter at the present time.

NSA 20-898 Thyrogen (thyrotropin alfa) Genzyme Corportation Date of submission: December 12, 1997

Addendum to Medical Team Leader's comments on NDA: June 12, 1998

In the original NDA submission, the sponsor maintained that Thyrogen testing, utilizing whole body radioiodine scanning and thyroglobulin (Tg) testing was comparable, with regard to diagnostic accuracy, to testing after thyroid hormone withdrawal. As such, proposed was to label the drug such that Thyrogen stimulation testing would be recommended as a substitute for withdrawal that had nearly equivalent diagnostic accuracy while sparing the morbidity associated with hypothyroidism after withdrawal.

Review of the data submitted in the NDA revealed that, indeed, Thyrogen whole body scanning tended to underdetect disease relative to withdrawal scanning. The study series included a number of patients with metastatic disease in whom the Thyrogen scan showed minimal or no disease. Furthermore, thyroglobulin levels after Thyrogen stimulation tended to be significantly lower than those after withdrawal, and, importantly, there was no clear correlation between the two. These findings suggested that 1) Thyrogen stimulation using the protocol recommended in labeling was inconsistent and 2) therefore could not be relied upon to assess accurately the location and extent of residual or recurrent local or metastatic well-differentiated thyroid cancer. In short, Thyrogen stimulation testing yielded data that were quantitatively different from those after withdrawal and therefore could not be used in place of withdrawal data to guide clinical decision making in patients with well-differentiated thyroid cancer.

Because of the above, this reviewer's initial recommendation was non-approval of the drug for the

proposed use.	action was non-approval of the drug for the

Assuming that final agreement can be reached on labeling as described above, this reviewer recommends approval of Thyrogen for use as an adjunct to withdrawal in the follow up of patients with well-differentiated thyroid cancer.

Recommendation Code: AP

cc: HFD-510 NDA Arch 20-898 HFD-510: Sobel/Temeck/McCort David G. Orloff, M.D.

Medical Team Leader

DMEDP/CDER/FDA

6-/2-78

memo To f. Le: NDN 20-898

NDA: 20898 Drug: Thyrogen Sponsor: Genzyme Date: 5/22/98 Proposed changes to Thyrogen labeling:

Clinical Pharmacology

Pharmacodynamics

DRAFT LABELIAG

Clinical trials

replace entire section with:

DRAFT CABELING

ADDENDUM TO Review

NDA: 20,898 Drug: Thyrogen Sponsor: Genzyme Date: 4/24/98

Corrections/Clarifications to Dr. Temeck's Clinical Review:
1. Page 8: footnote "C" also applies to the patient in whom the withdrawal scan stage was 2 and the Thyrogen scan was stage 1.

Therefore, on page 9, footnote "C" should read: "These 3 patients..."

2. Pages 22-24, tables 1-6 are a comparison of the withdrawal and Thyrogen scans.

Page 22, table 1, the 9 discordant scans in arm I and the 8 discordant scans in arm II, refer to the scans favoring

APPEARS THIS WAY ON ORIGINAL

cc. NDA 20,898 Arch
HFD-510. Div. file
HFD-510: Dr. Orloff/ Mr. McCort

Jean Temeck, M.D!

(S)
4-24-98



ORIGINAL

NEW CORRESP

GENZYME CORPORATION ONE KENDALL SQUARE CAMBRIDGE, MA 02139-1562, U.S.A. 617-252-7500 FAX 617-252-7600

Ref. NDA #20-898
Thyrogen® (thyrotropin alfa)
Amendment 010

ECT 0 8 1998

Dr. Solomon Sobel
Division of Metabolism and Endocrine Drug Products
Food and Drug Administration
Parklawn Bldg., HFD-510, Rm. 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: Thyrogen® NDA: Complete Response to Approvable Letter

Dear Dr. Sobel:

Reference is made to the Thyrogen® NDA (20-898) submitted December 12, 1997, the September 15, 1998 FDA Approvable Letter and the subsequent September 16, 1998 Intent to Amend general correspondence to NDA 20-898.

In accordance with 21 CFR 314.110(a)(1), the purpose of this correspondence is to provide a complete response to the September 15, 1998 approvable letter to NDA 20-898.

As recognized in the September 15, 1998 approvable letter, please incorporate the September 3, 1998 Minor Labeling Amendment as part of the review of this approvable letter response.

Please find the following documentation included in this complete response:

Requested a	locumenta	tion rega	rding T	SH Bio-assay	
Attachment	1: Addre	sses Poir	t 1 of A	nnrovable I	

Attachment 1: Addresses Point 1 of Approvable Letter: A proposed protocol for establishing an in-house working reference standard to be used for product release. This protocol was submitted for initial review on September 22, 1998 and found acceptable at the October 2, 1998 teleconference. (Please refer to Commitment 3 for timeline).

Attachment 2: Addresses Point 2 of Approvable Letter: Release and stability data (ED₅₀ values) obtained from our current for all batches tested.

There is No haw Jafory

- information

/S/

REVIEWS COMPLETED
CSO ACTION:
LETTER N.A.I. MEMO
CSO INITIALS DATE

C HIGHHISTORY



NDA 20-898/Amendment 010 October 7, 1998 Page 2

Attachment 4:	limit for the release specification including the justification for upper and lower limits of
	justification was submitted for initial review on September 22, 1998 and found acceptable at the October 2, 1998 teleconference.
Written comm	<u>itments to NDA 20-898:</u>
1. We commi	t to use the WHO reference standard, with revised in vitro specific
of the two	ay (21 data points) and an acceptance criteria of ≥ 4 IU/mg for testing current lots of drug product and any future lots until a valid, in-house ference standard is established following the protocol provided in
and specific	t to revising the current stability protocol to include all changes in tests cations. We are providing in Attachment 5 a draft stability protocol ides the expected changes to the
	As discussed in the October 2, 1998 teleconference, we commit to
run the	at 0, 6, 12, 18, and 24 months followed by
annual testi	ng thereafter.
3. We commit	to provide the validation data for the
used to qua approval.	lify a Genzyme reference standard no later than 6 months after NDA
Updated Safety	Information:
Attachment 6:	Updated Safety Report to NDA 20-898. This updated report integrates all safety information through August 31, 1998. All new safety information comes from the Compassionate Use program and therefore we have updated Section 4.0 of the ISS.

Introductory Promotional Materials:

One copy of the introductory promotional materials for Thyrogen. This promotional material is based upon the labeling submitted in our September 3, 1998 Labeling Amendment. Two copies of this promotional material are being provided directly to the Division of Drug Marketing, Advertising and Communications (See enclosed binder of DDMAC submission.).

NDA 20-898/Amendment 010 October 7, 1998 Page 3

It is our intention and understanding based upon the October 2, 1998 teleconference that the information provided in this amendment constitutes a complete response to the September 15, 1998 approvable letter to Thyrogen. We are looking forward to an expeditious review and final approval of NDA 20-898.

Should you have any questions or need additional clarification concerning this correspondence, please do not hesitate to call me at 617-374-7425.

Sincerely

Ilze Antons, M.S.

Manager, Regulatory Affairs

Desk Copies: Steve McCort, Regulatory Project Manager (4 Review Copies)

REQUEST FOR TRADEMARK REVIEW



To:

Labeling and Nomenclature Committee

Attention:

Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

Division of Metabolism and Endourine products.

Attention: Dun-Gong War

Phone: 301-827-6387

Date:

3/3/98

Request for Assessment of a Trademark for a Proposed New Drug Product

Proposed Trademark: Thyrogen

NDA/ANDA# 20-898

Established name, including dosage form:

Thyro tropin alfa, injection

(Thyrold Shoulather hormone)
Other trademarks by the same firm for companion products:

Indications for Use (may be a summary if proposed statement is lengthy):

for the detection of thyroid remnants and thyroid causer in post-thyroidectomy patients on hormone suppression through

Initial Comments from the submitter (concerns, observations, etc.):

APPEARS THIS WAY ON ORIGINAL

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. December 95

CDER LABELING AND NOMENCLATURE COMMITTEE

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Established Name XXX Satisfactory	Low	Medium	High
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MEMORANDUM OF TELEPHONE CONFERENCE MINUTES

Meeting Date: October 23, 1998

Time: 11:00 am Location: 14B-56

Application: Thyrogen

NDA: 20-898

Type of Meeting: Labeling

Meeting Chair: David Orloff, M.D., Medical Team Leader

Meeting Recorder: Steve McCort, Project Manager

FDA Attendees, titles, and Office/Division:

David Orloff, M.D., Medical Team Leader, DMEDP, HFD-510 Jean Temeck, M.D., Medical Reviewer, DMEDP, HFD-510 Jayne Peterson, Reviewer, DDMAC, HFY-12 Sonia Castillo, Ph.D., Statistics Reviewer, HFD-720 Steve McCort, Project Manager, DMEDP, HFD-510

External Constituent Attendees and titles:

Allison Lawton, Vice President, Regulatory Affairs Ilze Antons, Senior Regulatory Manager, Regulatory Affairs Kevin McEllin, M.D., Director, Clinical Affairs David Meeker, M.D., Vice President, Medical Affairs P.K. Tandon, Ph.D., Senior Director, Biometrics

Background:

This meeting was called at the request of FDA to discuss the September 3, 1998, labeling submitted to the file for NDA 20-898. The Division submitted by FAX comments/revisions to the labeling. The firm faxed a revised copy of the labeling on October 21, 1998, incorporating the requested revisions from the Division's October 20, 1998 FAXED comments. In their request the firm asked for clarification regarding patient numbers in the first paragraph of the Thyrogen Tg results: Overall Sensitivity section. Their question for the reviewer (either Dr. Jean Temeck or Dr. Sonia Castillo) was to identify the patient numbers of the two patients that were dropped (one in the 2 dose and one in the 3 dose regimen).

Meering Minutes
Page 2

Meeting Objectives:

- 1. Review and Discuss the September 21, 1998 revised draft labeling FAXED to FDA.
- 2. Discuss the reasons why the response to the Not Approvable letter was determined to be a class 2 submission requiring a 6 month action from FDA, rather than a class 1 response requiring a 2 month action.

Discussion:

APPEARS THIS WAY

Regulatory:

1. Allison Lawton asked the Division why the firm's October 8, 1998, resubmission to the September 15, 1998, Approvable letter, for NDA 20-898 was classified as a class 2 response requiring a 6 month review rather than a class 1 response requiring only a 2 month review and response from FDA? Ms. Lawton stated that Dr. Bilstad had been contacted and could not comment at the time, but would look into the issue. Dr. Orloff will follow-up on this issue and get back to Genzyme.

Labeling:

The following agreements were made by FDA and Genzyme to the October 21, 1998, labeling FAXED to the Division (see FAXED copy of the package insert):

- 1. Under Thyroglobulin Results: Overall sensitivity of Thyrogen Tg Testing Alone and in Combination with Radioiodine Imaging, paragraph 1:
 - * line 5, firm has a question regarding the numbers. Firm asked if the numbers were really 54/122? rather than 54/121). Jean Temeck will get back to Kevin McEllin on Monday October 26, 1998.

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	Paragraph 1, line 6, the last two sentence that read	
	Should now read,	
	er Considerations for Use of Thyrogen, page 7:	
	Paragraph 3, line 6 which reads	
	should now read,	
Jnde	r PRECAUTIONS, General	APPEARS THIS WAY
	Paragraph 2, line 3, which reads,	on original
	should now read,	
	Paragraph 6, line 3, the last two sentences which read,	
1		

5.	Under ADVERSE REACTIONS section,
	* Paragraph 6, which reads,
	needs to be revised with a stronger statement which includes more details about the
	patient and that the MI event was clearly related to the hyperthyroid condition with the 4 Thyrogen injections.
6.	The firm wishes to submit a supplement regarding the sensitivity of the Tg assay used in the trials compared to the to the
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Decisions (agreements) reached:

- The Firm and FDA agreed with the revised draft labeling dated September 20, 1998
 FAXED to FDA (which included revised comments from FDA) except for the following:
 - a. Under Thyroglobulin Results: Overall sensitivity of Thyrogen Tg
 Testing Alone and in Combination with Radioiodine Imaging, paragraph
 1, line 5, the firm has a question regarding the numbers. Is it really 54/122?
 (rather than 55/124). Two patients which had unresolved scan ratings were left out by FDA in the final numbers. Dr. McEllin will check on these patients and give Dr. Jean Temeck of this Division an update on these patients on Monday October 26, 1998.
 - b. Under ADVERSE REACTIONS section, paragraph 6 will be rewritten to include a stronger statement regarding the relationship of the MI adverse event in the 77 year old man to hyperthyroidism occurring after 4 injections of Thyrogen over 6 days.
 - C. Under ADVERSE REACTIONS section the Table "Summary of Adverse Events During Controlled Studies (≥1%), Number of patients with Adverse Events, the numbers and % of patients in the table should be reversed with the % of patients first followed by the number of patients. (This was communicated in a separate telephone communication on October 23, 1998)

Meeting Minutes Page 6

Action Items:

	<u>Item</u>	Responsible Person	Due Date	
1.	Dr. McEllin will communicate with Jean Temeck regarding the two patients in the Thyrogen Tg results in the Clinical Pharmacology section of the PI.	Dr. McEllin, Genzyme	October 26, 199	8
2.	The firm will communicate with FDA on the remaining labeling issues before Submitting their labeling amendment to the NDA.	Ilze Antons. Genzyme	?	
	PREARS THIS WAY ON ORIGINAL	Minutes Preparer		10-29-98
		Chair Concurrence:	/\$/	10-30-98

Attachments/Handouts:

Concurrence: JTemeck 10-27-98/DOrloff 10-28-98/SCastillo 10-28-98

cc: Original

HFD-510/Div. Files

HFD-510/CSO/SMcCort

HFD-510/SSobel/DOrloff/JTemeck

HFD-720/SCastillo

HFY-12/JPeterson

Drafted by: smm/n20898.t12

final: smm/n20898.t12

MEETING MINUTES

MEMORANDUM OF TELEPHONE CONFERENCE

Meeting Date: October 2, 1998

Time:

10:00 am

Location:

PKLN 14B-56

Application: NDA 20-898; Thyrogen

Type of Meeting:

Chemistry Issues

Meeting Chair:

Duu-Gong Wu, Ph.D.

Chemistry Team Leader

Meeting Recorder:

Steve McCort

Project Manager

FDA Attendees, titles, and Office/Division:

Duu-Gong Wu, Ph.D., Chemistry Team Leader, DNDC 2 Steve Koepke, Ph.D., Deputy Director, DNDC 2 John Gibbs, Ph.D., Chemistry Director, DNDC 2 Yuan Yuan Chiu, Ph.D., Deputy Director, ONDC Steve McCort, Project Manager

Genzyme Attendees and titles:

Alison Lawton, Vice President, Regulatory Affairs
John McPherson, Ph.D., Senior Vice President, Cell and Protein Therapeutics
Edward Cole, Ph.D., Protein Therapeutic Development
Robert Mattaliano, Ph.D., Director, Bioanalytical Development
Kim Raynor, Associate, Regulatory Affairs
Ken Edmonds, Regulatory Affairs
Ilzi Antons, Manager, Regulatory Affairs

Background:

This meeting was called as a result of the approvable letter dated September 15, 1998. The telephone conference was requested in a September 22, 1998 letter to the Agency to discuss the chemistry deficiencies addressed in that letter. Specifically the firm requested clarification of points 1, 3, and 4 and clarification of point 2 regarding the commitments.